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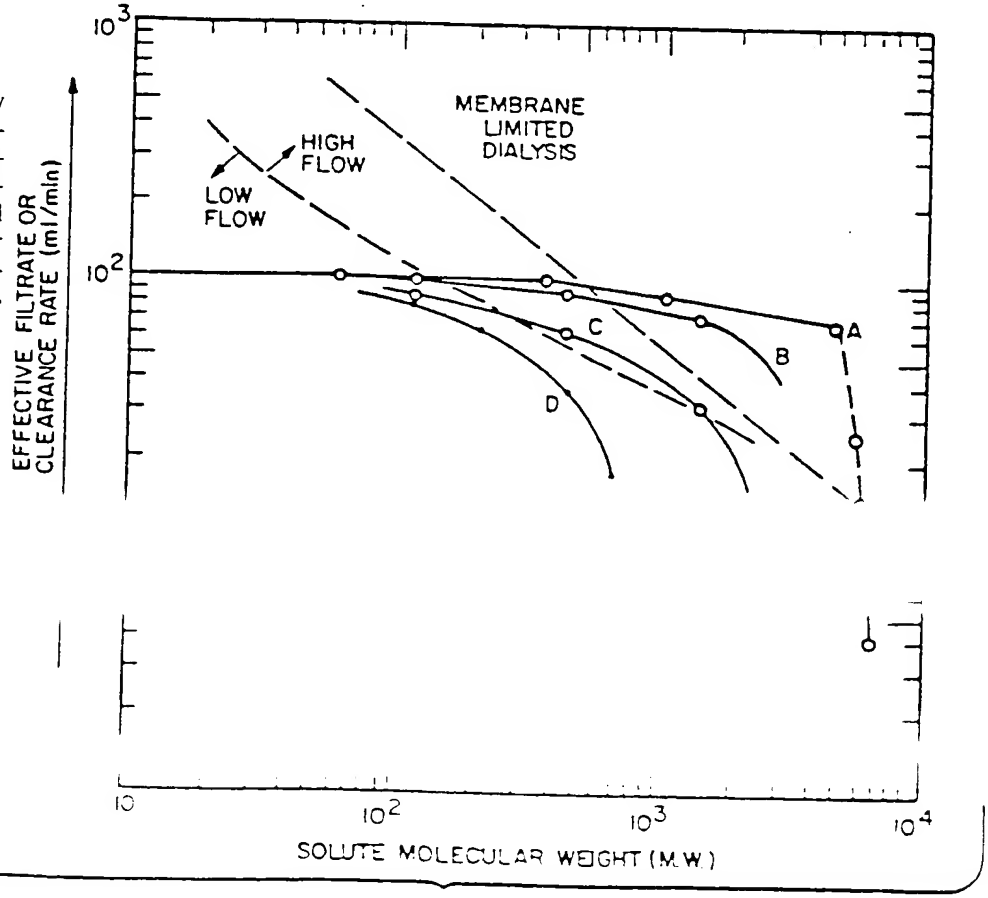
(57) Abstract

Method for treating body fluids like blood or its components including apparatus suitable therefor. A preferred embodiment comprises an artificial kidney apparatus suitable for cleansing the bodily blood without the need for large quantities of pure water as required by existing kidney apparatus.



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METHOD AND APPARATUS FOR TREATING BLOOD AND THE LIKE

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates generally to an improved method for filtering biological fluids including blood and, more specifically, to a method for filtering the blood of the kidney patient in order to remove accumulated waste components.

2. Description of the Prior Art

The best known methods for removing waste materials from blood comprise various forms of dialysis. One involves passing the blood on one side of a semipermeable membrane and passing a dialyzing fluid containing suitable electrolytes on the other side of the membrane (process of hemodialysis). A portion of the blood water and low to moderate molecular weight waste materials diffuse through the membrane into the dialyzing fluid which must be continuously supplied in order to avoid electrolyte and toxin build-up which would stop or reduce the transfer of such materials from the blood. While units based on this principle are widely available and fairly reliable, they have several disadvantages. The system as a whole is relatively complex and cannot be made readily portable. In addition, a trained operator is required. Treatment typically involves a

a week to remove the accumulated toxic waste build-up, regulate electrolytes in the body and remove any excess water. In

addition to the expense of the treatment there is a problem that such a routine allows a much greater build-up of toxic waste in the body than does the normal kidney function so that there is a severe trade-off between efficacy and expense, including inconvenience.

Because of the above disadvantages of the dialysis method, researchers for many years have sought that replacement which would be more portable, might lead to more frequent use, and reduce the need for bulky, complex equipment and trained operators. One method which resulted from these efforts is described in the Markovitz U.S. Patent 3,483,867. That patent teaches the filtration of blood through a filter membrane under pressure to remove a portion of the water and associated waste materials, thereby eliminating the need for dialysis fluid and its attendant complications. Among the several variations of this method, one process includes passing the filtrate with its associated waste materials through a system of cartridges and secondary filters to selectively remove the waste materials and adjust the electrolytes. This purified fluid is then continuously returned to the bloodstream eliminating the need for large quantities of pure make-up water. Only minor replenishment of electrolytes might be required so that the general approach is capable of producing a portable unit suitable

filtrate system for protection against bacterial and/or pyrogenic contamination. Another could be to trap intermediate sized species which pass through the first blood filter (hemofilter) but would be rejected (retained) by the secondary filter. This application is shown schematically on Figures 1 and 2 where the different rejection characteristics of two filters are converted into a process for removing the intermediate sized species.

Despite large amounts of work on the general concept, the hemofiltration technique described above has never become practical because known filtration techniqes do not permit the required waste removal rate in order to cleanse the fluid (e.g. blood) in a reasonable time with a low membrane area without clogging the filter membrane with the rejected blood material. This undesirable accumulation both reduces the removal rate efficiency and modifies the response of the filter. In the artificial kidney application the changes with accumulation would be both lowered filtration efficiency and increased rejection of dissolved compounds. While hemofiltration is potentially superior to hemodialysis, such changes can make it worse than hemodialysis.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide an

characteristics may be achieved with lowered membrane areas

and/or treatment times.

It is the further object of this invention to provide an improved method for efficient filtering of blood, plasma or other body fluids whereby practical filtrate rates are obtained and components of predetermined molecular weight or size are removed in the filtrate.

It is still another object of this invention to provide an improved artificial kidney machine which allows removal of water together with low and moderate molecular weight toxic components in order to clear waste materials from a kidney patient.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with one embodiment of this invention, efficient ultrafiltration is achieved by spiral geometry filter means with the blood flow parallel to the axis of the spiral and filtrate removal along the spiral in order to provide efficient blood filtration.

In accordance with another embodiment of this invention, the ultrafiltration method includes the use of a spiral filter and recirculation through the filter of a major fraction of the blood leaving the filter.

In accordance with yet another embodiment of this invention,

to achieve optimal filtration characteristics.

The foregoing and other objects, features and advantages of the invention will be apparent from the following, more particular description of the preferred embodiments of the invention, as illustrated in the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows the rejection characteristics of exemplary filters for use in this application.

Figure 2 shows schematically a portion of a filter system for removal, as an example, of middle molecular weight material from a feed fluid.

Figure 3 depicts important components of human blood including waste materials as a function of their molecular weight or cell size.

Figure 4 shows the filtrate rate versus pressure characteristics of a filter suitable for removal of low and middle molecular weight materials from the blood.

Figure 5 shows the clearance or removal rate versus the molecular weight of dissolved species as a function of the quantity of rejected materials (e.g. very high molecular weight proteins and/or cells) present on the filter membrane surface.

Figure 6 is a schematic representation of an ultrafiltration system suitable for blood and the like.

Figure 8 illustrates the effect of recirculation through the convective feed path of the filter on its efficiency as a function of the blood composition and operating variables.

DETAILED DESCRIPTION

Referring to Figure 3, the approximate distribution of constituents which make up human blood is shown as a function of either molecular or cell size. The major fractions A and B, spanning low and moderate molecular weights, include the electrolytes and at least a major portion of the toxins removed by the normal kidney. A third and fourth major fractions, C and D, of the blood have larger molecular weights and include proteins and antibodies. Fractions A, B, C and D together constitute the plasma portion of blood. The D fraction comprises molecular weights which range from approximately 45,000 to in excess of one million. Primarily platelets, red cells and white cells (the formed elements) exist in blood above the D fraction range.

Because of the relatively large molecular weight spacing between the plasma proteins (Fraction D) and Fractions A and B, ultrafiltration has the potential to permit selective removal of undesired constituents without disturbing the rejected major fractions (Fraction D and the formed elements). For example,

[illegible] of blood through a membrane having a pore size

corresponding to roughly a molecular weight in the range of 1,000 to 10,000 MW creates a filtrate which contains primarily Fractions A and B in solution. It is then possible to treat this solution in subsequent steps (e.g. ion exchange, sorption, a second or third filter, etc.) to purify and adjust the filtrate solution. This allows the return of the cleansed and adjusted filtrate to the patient. Sequential filtration and processing of filtrate simulates the action of the normal kidney. Similarly, the use of a filter membrane having a pore size of between 0.1 and 0.9 microns can separate the plasma from the cellular formed elements (platelets, red cells, white cells). This would allow either the processing of plasma proteins for a wide variety of purposes (e.g. combating immune deficient diseases) or the further separation and/or treatment of the different formed elements. One broad example is the selective removal of a single unwanted component of middle molecular weight shown schematically on Figures 1 and 2. Because most present filters have a distribution of pore sizes, rejection may not occur precisely at and above a given particle size or molecular weight, but rather increases over a limited range of particle sizes or molecular weights. To the extent that this range can be made to coincide with low concentration regions of the blood constituent spectrum, separation of the major blood constituents is possible. Any

particle suspensions including lymph fluids, animal blood, sewage components, milk and/or dairy product suspensions such as whey, and microbial suspensions.

In the so-called batch filtration process, the feed fluid is passed essentially normal to the plane of the filter. For a fluid such as water containing suspended sand, batch filtration is feasible as a semi-continuous process because the water can continue to flow through the sand which builds up on the upstream side of the filter and filtration continues with only moderate increases in pressure. Batch filtration is not suitable for continuous use with whole blood because the larger constituents effectively clog the filter and engender large pressure increases for a given filtrate rate. Filtration of blood can be made more efficient and continuous by the use of a convective filter where the feed fluid flows approximately parallel to the filter membrane and thus tends to carry off those constituents of the fluid which decrease the filtrate rate. The required flow of filtrate perpendicular to the filter membrane can still cause problems of clogging. The general problem is discussed at greater length in the co-pending patent application of Dorson, Pizziconi, and Markovitz entitled "Method and Apparatus for High-Efficiency Filtration of Complex Fluids", filed on April 13,

clogging and membrane pore clogging. Surface clogging is caused

by rejected materials which accumulate on the surface (feed fluid side) of the filter membrane. The amount and density of this type can be controlled by the methods, devices, and procedures described or referenced in this disclosure. The second type of clogging refers to constituents of the blood or other body fluids becoming immeshed within the membrane ultrastructure. This type is, in general, less affected by convective events within the feed channel although there is still a possible minor contribution from events within the feed channel. The basic membrane filtration characteristics would be altered in the latter case wherein a different straight line buffered saline limit could be encountered (e.g. the straight line of Figure 4 would be rotated clockwise). The initial technical concepts on membrane pore clogging as well as other limit phenomena were presented in the paper "Quantitation of Membrane-Protein-Solute Interactions during Ultrafiltration" in Transations of the American Society for Artificial Internal Organs, Vol. 24, pg. 155, 1978. A more generalized and complete description of multiple limit phenomena supplemental to this disclosure was published in July, 1980 as the chapter entitled "Ultrafiltration of Plasma and Blood" in the book Advances in Biomedical Engineering, Part II, edited by D.O. Cooney (Marcel Dekker, Inc., New York and Basel).

of filtration

transmembrane pressure relationship. In that figure, filtrate rate is linearly proportional to pressure for a "buffered saline" solution. However, when proteins similar to those found in blood are added to the feed fluid, linearity fails and the pressure deviates from the ideal limit very dramatically at and above a certain filtrate rate determined by the nature of the feed fluid, the filter membrane, and the flow conditions (as examples). Figure 4 also shows graphically the definition of efficiency used herein; efficiency is the ratio of the filtrate rate, N_B, on the non-linear curve to the filtrate rate, N_A, on the linear buffered saline curve at the same transmembrane pressure. Note that the efficiency decreases at the pressure is increased. Low efficiency conditions at high pressures can result in gel or precipitate formation on the membrane surface as denoted by the indicated forbidden operational area.

Heretofore, attempts to treat blood by ultrafiltation have been either unsuccessful or of limited success because of inefficient filters. There are two major problems. First, while efficiency may be enhanced by moving from say point D to point B in Figure 4 by reducing the pressure and filtrate rate, the rate becomes unacceptably low and may only be increased by making the filter large. In known configurations of filters for blood applications, area enlargement increases the total amount of

effects. As regions of the filter begin to become ineffective, either the filtrate rate drops or the transmembrane pressure (TMP) increases. The second major problem is that when the filter is operated inefficiently, the composition of the filtrate is modified. This is illustrated by Figure 5 where it may be seen that as the conditions change from points A (no protein) to B, C, and D (increased pressure, protein deposit, and density) in Figure 4 the filtrate includes less and less of the middle molecular weight species (e.g. Fraction B of Figure 3). In the case of the kidney application, for example, the clearance rate can drop so low (e.g. curve D) that conventional hemodialysis rates (shown for comparison purposes) are more efficacious than hemofiltration clearances.

Figure 6 shows schematically a preferred embodiment of this invention in the form of a kidney machine suitable for long-term therapy. Input blood is extracted, as an example, from the patient's artery or internal fistula/shunt and passes to the input port 30 of the apparatus. The blood then passes to input port 3 of the convective ultrafilter 1. A pressure differential, TMP, across the filter membrane 9 causes water and waste components to separate from the blood circuit chamber 4 and pass through the membrane to the filtrate plenum 6. A portion of the filtrate withdrawn from the filter 1 may be discarded as

remainder of the filtrate

(e.g. cartridges, secondary filters, etc.) which removes waste materials (end products of metabolism, toxins) and adjusts the electrolyte concentration. The output of the processor 11 consists of water, electrolytes and nutrients at a rate F which is a fraction f of the input blood flow rate FF. This purified stream is returned to the patient and/or to the filter 1 as described in more detail hereinafter. That portion of the input blood which is not withdrawn as filtrate passes through and out of the convective filter at output port 5 of the filter and is returned to the patient's vein by way of apparatus output port 50.

Filter 11 preferably comprises a series of filters/cartridges each especially adapted to remove or change one or more of the plasma components. Suitable filters/cartridges are known to those skilled in the art and will not be described in detail here. Small quantities of makeup electrolytes, (such as calcium and magnesium), nutrients (such as glucose and/or amino acids) or medications (such as sodium bicarbonate, vitamins, etc.) may be added to the filtrate stream F which preferably also passes through a final bacterial filter before being returned to the patient; these details are not specifically shown in Figure 6.

In order to achieve and maintain efficient ultrafiltration

configured and operated using one or more forms of augmentation

herein defined as:

(1) surface perturbations in narrow flow channels

(2) irregular but controlled channel geometries

(3) membrane charge characteristics (repellant)

(4) secondary flow induction by channel inserts (screens, ribbons, etc.)

(5) externally applied forces and/or motions (physical movement, ultrasound, electrical potential, pressure perturbations, pulse flow, etc.

(6) staging of devices

(7) independent manipulation of flow rates in the device

(8) preferred geometries in combination with augmenting methods

(9) independent control of biochemical and biophysical conditions during filtration.

Referring now to Figure 7, various views of portions of a suitable filter are shown. The input blood FF passes through the length L of the filter between the membrane elements 90. Elements 200 schematically represent a blood screen which serves to separate the membrane elements 90 by an appropriate distance, to introduce some resistance to flow into the blood path (whereby uniform flow is obtained) and to induce secondary flows which membrane clear. The model shown contains the

flow of the filtrate towards the permeate collecting

For the kidney machine, the total area of the membrane 9 o Figure 6 is desirably on the order of 0.7 m^2 for average adu intermittent application. The height H of the blood flow path is desirably in the range 0.25 to 1 mm; too small a val introduces excessive resistance into the blood flow path whil too large a value results in inefficient filtration condition and an impractically large filter.

In order that the filter 1 achieve and maintain efficiency, it is imperative that any impediments in the convective path do not appreciably reduce the effective width of the channel (i.e. active membrane) below its nominal value W. For example, if the filter consists of multiple hollow fiber membranes in a parallel arrangement, each with a bore diameter H, rapid plugging of a substantial number of the fibers can occur due to feed fluid concentration and the effective area is unacceptably diminished. Referring to Figure 7A, if a local impediment occurs in the channel, the blood must be able to continue to flow both upstream and downstream of the impediment. A rough geometrical criterion for such a condition is that W should be at least large as L. This requirement is most easily met by spiral filters, which are also compact and relatively easy to fabricate. Referring now to Figures 7B and 7C, there is shown a cross-section of a spiral filter. The membrane 9 (Figure 6) comprises an envelope with the backing 400 fr

66. The envelope and the blood screen 200 are both wound around a central hollow mandrel 500 which serves as a conduit for the filtrate stream F. The porous backing 400 from envelope 9 opens only onto holes 300 leading to the hollow portion of the mandrel 500; the filtrate stream passes from the filter unit 1 through the axis of the mandrel 500. Similarly, the blood passes through the filter perpendicular to the drawing. More details of the construction of a spiral filter may be found in the Westmoreland U.S. Patent 3,367,504, which describes its use for the desalinization of sea water.

Several different combinations of spiral wound construction have resulted in achieving the high efficiency necessary for this application. In looking at the cross section perpendicular to the flow area, models have contained a blood side spacer, then the cast membrane, and then a filtrate mesh spacer. By casting the membrane directly onto a porous, woven, incompressible substrate, the filtrate spacer was eliminated, so that existing construction would consist of the blood side spacer and the membrane shown in the drawings herein. The membrane envelope is made by gluing the edges of the porous substrate together with a water-resistant adhesive, such as the urethane glue made by the Hexel Corporation. Other adhesives used in the module [illegible] include medical grade silicone (e.g. Dow Corning

strategies common in the field. [illegible]

been Dacron tricot or sailcloth stiffened with a melamine resin, while other materials, such as the DuPont Reemay, have also been used with success. Two types of membranes have been developed for this purpose with, apparently, equivalent results. The first type is an asymmetric cellulose acetate somewhat similar to the reverse osmosis membranes developed for desalinization. Unlike the reverse osmosis application, changes had to be developed in order to allow free passage of electrolytes while rejecting the major plasma proteins. The changes in the process were either in formulation and annealing conditions or just in the annealing conditions. Two such formulations have been the glycerin perchlorate cellulose acetate formulation with altered annealing and the cellulose acetate annealed for short periods of time at less than or equal to 80° Centigrade. The main end point is to eliminate passage of molecules greatly in excess of 5,000 molecular weight, thus preventing the passage of at least the large proteins starting at 45,000 molecular weight. Acceptable rejection criteria is shown as line A on Figure 5. The exact annealing conditions will change with different cellulose acetate formulations and still produce an acceptable membrane. The second type of membrane that can be used in hemofiltration is a modification of the newer, thin film composite reverse osmosis technology. The thin film composite

described above (substrate), a polysulfone intermediate membrane, and a thin top film (200-500 Angstroms) on top of the polysulfone. One top film for reverse osmosis has been a polyamid formulation. The modifications for hemofiltration can be either one of two types. The first is to cast a sufficiently thick polysulphone film with pore sizes to yield the rejection characteristics given on Figure 5. Note that these rejection characteristics given as curve A on Figure 5 would represent an acceptable transmission of larger molecules for hemofiltration purposes with the intent for artificial kidney purposes to transmit molecules normally present in urine. A concomitant membrane criteria would be insignificant passage of molecules at and above 45,000 molecular weight. This is better understood with references to Figure 3, which shows the spectrum of molecules and formed elements in blood. The second modification of the thin film composite reverse osmosis technology would allow a thinner casting of the polysulfone base with an even thinner top film than is used in reverse osmosis. Again, the criteria is easy passage of electrolytes and end products of metabolism with insignificant passage of the larger plasma proteins. All of the modifications outlined above are easily accomplished by technical personnel well versed in membrane technology.

In order to achieve efficient hemofiltration, the blood side

commercial screens [illegible]

promoting removal of rejected material away from the membrane surface. Conversely, extremely thin screens can result in too much pressure drop, which detracts from the transmembrane pressure differential. One spacer that has worked is the Vexar, made by DuPont (polyethelene), with 12 strands to the inch and measuring a total thickness of approximately 25 mils. (0.025 inches). The preferred orientation is to have the mesh lines at an approximate angle of 45° to the flow direction as shown in Figure 7A.

A preferred casting material to enclose the spiral filter and direct the blood and filtrate streams is polycarbonate or an equivalent biocompatible material. The same material has been used for the filtrate collection tube onto which the rolled spiral assembly is wound. The wound assembly is sufficiently smaller than the inside diameter of the polycarbonate housing, to enable potting of the wound assembly into the polycarbonate shell using medical grade silicone adhesive. Dimensions applicable to hemofiltration are a membrane width of 10 inches with a wound assembly diameter of 2 and 2/3 inches. This yields an effective membrane area considered to be a minimum for adult human intermittent application of 0.7 meters squared. Other details of construction are similar to existing spiral wound technology in the reverse osmosis field, with the exceptions of

A filter in accordance with the foregoing description will still not result in efficient hemofiltration unless it is operated as now described. It has been found essential for maintenance of efficiency to recirculate a large fraction of the blood exiting the filter at port 5 by reintroducing it at input port 3 at recirculation rate R times the input blood flow rate FF. R must be substantially larger than 2 with a nominal FF of 200 to 250 cc/min.; values on the order of 3-8 are required to assure high efficiency with the filter membranes and devices used hitherto and described hereinbefore. While there is at present no comprehensive and exact theoretical basis for the relation of the value of R to the filter parameters and blood composition, most factors are known and at least two factors are believed substantial. First, the use of large amounts of recirculation R enhances the compositional homogeneity of the blood along the length of its flow path through the channel 4. A typical blood input flow rate range is 200-250 cc/minute with a typical filtrate rate of 80 cc/minute. Without recirculation, then, the plasma portion of the blood would be depleted of approximately half of its water by the time it reached output port 5. For example, if R = 4, then the filter input flow rate is in the range 1000-1250 cc/minute so that withdrawal of 80-100

increased rate of flow through the filter with recirculation

apparently results in an increased scrubbing action on the filter membrane whereby its clogging proclivity is reduced. As the blood access limited flow rate is increased, the value of R can be decreased and still achieve high efficiencies.

Figure 8 gives data illustrative of the effect of the recirculation ratio R on the efficiency of the filter. Efficiency is very low without recirculation (R = 0) and then rises dramatically. In general, the larger the ratio of the operating variable, FF x R/T.P., the higher the filter efficiency. This efficiency relationship is further dependent on HCT, PH, TMP, and fibrinogen levels for a given filter design, i.e. H, W, L and screen design. The limit value for the efficiency ranges above 80% and depends inter alia on the variables indicated as well as other factors listed on Figure 8. Because maximal efficiency may occur at positional values different from those of the patient's blood, efficiency may be maximized by differentially returning the filtrate flow F to the filter input port 3 and the patient blood return port 50. For example, for a non-anemic patient (HCT relatively high), it is desirable to return all of the filtrate flow F to the input of the convective filter 1. The above specification of geometries and operating conditions are based on adult human intermittent application. Specifications for continuous treatment of body

In addition to the preferred embodiments described above, the following is a review of typical applications of listed augmentation methods. Surface perturbations in narrow flow channels can be achieved in several ways. One is to have the membrane exposed to the feed channel containing surface irregularities which may, as an example, be achieved by casting the membrane over an underlying matrix which would promote the formation of the perturbations in the final membrane product. Another method is to have the membrane supported by an irregular plastic insert with the transmembrane pressure sufficient to deform the membrane over the perturbation typically moded into the plastic support. An example of irregular but controlled channel geometries would include tight coiling of the feed channel, having periodic or asymmetric surface waviness parallel to the flow, and folding of the flow channel again in a manner to induce flow diversion in the direction of flow. For feed fluids containing charged molecules or particles to be rejected, the membrane can be constructed to contain fixed repellant charges. In addition to the efficiency induction by screen covered in detail, a tubular blood channel can benefit by using a ribbon to produce spiral flow (secondary flows) in addition to axial flow through the tube. Examples of externally applied

[illegible] are not restricted to, the application

electrically induced with the insertion of electrodes [illegible]

the membrane or support structure. In this way, a polarization parallel to the filtrate flow aids in repelling the rejected materials away from the membrane surface. Electrodes have been formed by using metallized screens to support the membrane along with a metallized flow channel bounding surface opposite from the surface of the membrane. Another augmentation technique involves the use of ultrasound for improving filtration efficiency. Instead of the metallized requirement, the material must have, as an example, piezoelectric properties. To achieve ultrasound frequencies, discrete crystals would be required compared to only low frequencies available with single continuous sound drivers (e.g., reeds or electromagnetically driven diaphragms) in the feed channel. Ultrasound may be implemented in several ways, including crystals directly exposed to the feed channel. This is the most electrically efficient way of transmitting ultrasound frequency. It is also the least efficient in promoting filtration efficiency while posing the possibility of "heat" damage to the blood. A less electrically efficient way of producing ultrasound is to have the transducer face placed parallel to the direction of the feed flow, either in or underneath the membrane structure. Although less electrically efficient, the augmentation of filtration by the membrane is most effective with this orientation. Ultrasound

Ultrasound techniques include the use of a single frequency, frequency spectra, and combination of frequencies dependent upon the application. Examples of physical movement include a "washing machine" agitation, continuous rotation with special rotating seals or connectors, or linear vibration, all applied to the entire filtering module. Staging of devices includes the use of more than one device arranged in a parallel and/or sequential manner. This allows direct introduction of cleansed filtrate into the feed flow between each module. This dilutes the feed flow, allowing more efficient filtration in each module, but normally at the price of increased total surface area (more modules) with concomitant improvement in total clearance or effective filtration. These trade-offs are inherent in the implementation of staging and quantitative calculations can be made by individuals versed in controlling filtration phenomena. Staging may also be of the macrostage variety, in which selected reintroduction of filtrate can be achieved by design along an otherwise continuous flow channel. Staging is also meant to imply any method of intermittently "mixing up" the feed stream to eliminate any component polarization within the feed stream. Another variation of staging also found to be effective is the alternating of active and inactive filtering areas.

[illegible] mixing alluded

would be by diffusional processes in the case of rejected

molecules. With the simultaneous use of other augmenting methods, convective modes of transport could assist the diffusion. Independent manipulation of flow rates in the device include, generally, any additional pumping or flow action in addition to the simple throughput required to achieve practical filtration. Details have been given on the use of recirculation in one of the preferred hemofiltration designs, but the invention would also include mechanical oscillatory motions to cause vortex shedding and/or fluid replenishment from grooves perpendicular to the mainstream feed flow, as an example of preferred geometries in combination with other augmentation methods. The more direct example herein is in the use of spiral hemofilter modules with screens capable of inducing high efficiency in combination with recirculation of the exiting fluid back to the inlet. Since the hematocrit affects the production of optimum efficiency, variation of the reintroduction of filtrate between the module inlet and exit is also a method of improving the filtering efficiency, considered to be one of the biophysical condition embodiments. In addition to the methods already covered, independent control of biochemical and biophysical conditions includes the pH in the feed channel (more importantly at the membrane surface), control over the charge at the membrane surface, and the fractional filtrate (f)

While the invention has been particularly described and shown in reference to the preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and detail and omissions may be made therein without departing from the spirit and scope of the invention.

We Claim:

1. An apparatus for the filtration of predetermined molecular weight components from blood comprising convective filtration means for separation of said blood into a first fraction having high molecular weight components than said first fraction, said filtration means including at least one augmentation means for maintaining efficiency during said filtration.

2. An apparatus for the filtration of predetermined molecular weight components from blood, comprising convective filtration means for separation of said blood into a first fraction having high molecular weight components with cells and a filtrate fraction having lower molecular weight components than said first fraction, said means comprising spiral geometry augmentation means for maintaining efficiency during the period of said filtration.

3. A hemofiltration artificial kidney apparatus for the removal of toxic blood components from a patient's circulatory system, comprising, in combination:

means for receiving a blood stream from said patient;

convective filtration means for separation of said blood stream into a first fraction having high molecular weight components with cells and a filtrate fraction having lower

maintaining efficiency during said filtration;

auxiliary filtration means for treating said filtrate fraction by removing said toxic blood components; and

means for returning said first fraction and said treated filtrate fraction to the circulatroy system for said patient.

4. A hemofifltration artificial kidney apparatus for the removal of toxic blood components from a patient's circulatory system, comprising, in combination:

means for receiving a blood stream from said patient;

convective filtration means for separation of said blood stream into a first fraction having high molecular weight components with cells and a filtrate fraction having lower molecular weight components than said first fraction, said means comprising spiral geometry augmentation means for maintaining efficiency during the period of said filtration;

auxiliary filtration means for treating said filtrate fraction by removing said toxic blood components; and

means for returning said first fraction and said treated filtrate fration to the circulatory system of said patient.

5. In a hemofiltration artificial kidney apparatus, the improvement comprising spiral convective filtration means [illegible] of blood into a [illegible] components with cells and a filtrate fraction.

6. In a hemofiltration artificial kidney apparatus, the improvement comprising spiral convective filtration means for efficient separation of blood into a first fraction having high molcular weight components with cells and a filtrate fraction.

7. The apparatus of any of Claims 1-6, further comprising means for recirculating a portion of said first blood fraction through said convective filtration means to improve filtration efficiency.

8. The apparatus of any of Claims 1-6, further comprising means for recirculating a portion of said filtrate fraction through said convective filtration means to improve filtration efficiency.

9. The apparatus of any of Claims 1-6, further comprising first recirculation means for recirculating a portion of said first blood fraction through said convective filter means, and second recirculation means for recirculating a portion of said filtrate fraction through said convective filtration means, both of said recirculated portions improving filtration efficiency.

10. The apparatus of any of Claims 2, 4 or 6 wherein said convective filtration means comprises charged membrane means for repelling selected constituents in said blood.

11. The apparatus of Claims 1 or 2, further including second convective filtration means for separation of said filtrate fraction into a second blood fraction having intermediate molecular weight components and a third blood fraction having low molecular weight components.

12. The apparatus of Claim 3 or 4, where said auxiliary filtration means comprises second convective filtration means for separation of said filtrate fraction into a second blood fraction having intermediate weight components and a third blood fraction having low molecular weight components.

13. The apparauts of Claim 12, where said second blood fraction comprises either said toxic components or other consitituents for further processing or removal.

14. The apparatus of any of Claims 1-6 where said convective filtration means comprises membrane means having a pore size which allows transmission of molecules normally present in urine.

15. The apparatus of Claim 2 or Claim 4 where said spiral filter means comprise at least one other augmentation means for maintaining efficiency of said filter means during the period of said filtration.

16. The apparatus of Claim 15, further including at least one of said means for improving the efficiency of said filtration means.

17. A method for removing predetermind components from blood, comprising the steps of filtering said blood through a convective filter for separating said blood into a heavy fraction having high molecular weight components with cells and a filtrate fraction having lower molecular weight components than said heavy fraction, said filter having at least one augmentation means for maintaining the efficiency of said filtering during the period thereof.

18. A method of removing predetermined components from blood, comprising the step of filtering said blood through spiral convective filter means for separating said blood into a heavy fracation having high molecular weight components and a filtrate fraction having lower molecular weight components than said heavy fraction.

19. A method for removing toxic blood components from the circulatory system of a kidney patient, including the steps of:

withdrawing blood from said patient;

filtering said blood through convective filter means having at least one augmentation means to achieve high efficiency separation of said blood into a heavy fration having high molecular weight components with cells and a filtrate fraction having lower molecular weight components than said heavy fraction;

treating said filtrate stream to remove said toxic blood components; and

returning said treated filtrate stream and said heavy fraction to the circulatory system of said patient.

20. A method for removing toxic blood components from the circulatory system of a kidney patint, including the steps of :

withdrawing blood from said patient;

filtering said blood through spiral convective filter means to achieve high efficiency separation of said blood into a heavy fraction having high molecular weight components with cells and a filtrate fraction having lower molecular weight components than said heavy fraciton;

treating said filtrate stream to remove said toxic blood components; and

returning said treated filtrate stream and said heavy fraction to the circulatory system of said patient.

21. The method of any of Claims 17-20, further including recirculating a portion of said heavy fraction through said filtration means to improve filtration efficiency.

22. The method of any of Claims 17-21, furhter including recirculating a portion of said filtrate fraction through said filtration means to improve filtration efficiency.

23. The method of any of Claims 17-22, said method further

filter means to charged membrane

constituents in said blood.

24. The method of Claims 19 or 20 where said step of treating said filtrate stream comprises filtering said filtrate fraction through second convective filter means to provide an intermediate fraction having intermediate molecular weight components and light fraction having low molecular weight components.

25. The method of Claim 19, where said treatment step comprises discarding said intermediate fraction.

26. A method for removing plasma from blood, comprising the step of filtlering said blood through spiral convective filter means for separating said blood into a plasma fraction and a cellular fraction.

AMENDED CLAIMS

(received by the International Bureau on 17 September 1982 (17.09.82))

1. A hemofiltration artificial kidney apparatus for the removal of toxic blood components from a patient's circulatory system, comprising, in combination:

means for receiving a blood stream from said patient;

convective filtration means including membrane means and means to direct said blood stream substantially parallel to said membrane means for separation of said blood stream into a first fraction having high molecular weight components with cells and a filtrate fraction having lower molecular weight components than said first fraction, said filtration means comprising spiral geometry filtrate collection means;

auxiliary filtration means for treating said filtrate fraction by removing said toxic blood components; and

means for returning said first fraction and said treated filtrate fration to the circulatory system of said patient.

2. The apparatus of Claim 1, further comprising means for recirculating a portion of said first blood fraction through said convective filtration means to improve filtration efficiency.

3. The apparatus of Claims 1, further comprising means for recirculating a portion of said filtrate fraction through said convective filtration means to improve filtration efficiency.

4. The apparatus of Claim 1, further comprising first recirculation means for recirculating a portion of said first blood fraction through said convective filter means, and second recirculation means for recirculating a portion of said filtrate fraction through said convective filtration means, both of said recirculated portions improving filtration efficiency.

5. The apparatus of Claim 1, wherein said convective filtration means comprises charged membrane means for repelling selected constituents in said blood.

6. The apparatus of Claim 1, where said auxiliary filtration means comprises second convective filtration means for separation of said filtrate fraction into a second blood fraction having intermediate weight components and a third blood fraction having low molecular weight components.

7. The apparatus of Claim 6, where said second blood fraction comprises either said toxic components or other consitituents for further processing or removal.

8. The apparatus of Claim 1 where said convective filtration means comprises membrane means having a pore size which allows transmission of molecules normally present in urine.

9. The apparatus of Claim 1 where said spiral geometry means comprise at least one other augmentation means for maintaining efficiency of said spiral geometry means during the

10. The apparatus of Claim 9, further including recircultaion means for recirculating at least one of said first fraction and said filtrate fraction directly to and through said filtration means for improving the efficiency of said filtration means.

11. A method for removing predetermined components from blood, comprising the step of filtering said blood through filter means comprising spiral filtrate collection means for separating said blood into a heavy fraction having high molecular weight components and a filtrate fraction having lower molecular weight components than said heavy fraction.

12. A method for removing toxic blood components from the circulatory system of a kidney patient, including the steps of :

withdrawing blood from said patient;

filtering said blood through filter means comprising spiral filtrate collection means to achieve continuous high efficiency separation of said blood into a heavy fraction having high molecular weight components with cells and a filtrate fraction having lower molecular weight components than said heavy fraciton;

treating said filtrate stream to remove said toxic blood components; and

returning said treated filtrate stream and said heavy

13. The method of Claim 11 or Claim 12, further including recirculating a portion of said heavy fraction through said filtration means to improve filtration efficiency.

14. The method of Claim 11 or Claim 12, or Claim 13 further including recirculating a portion of said filtrate fraction through said filtration means to improve filtration efficiency.

15. The method of Claim 11, Claim 12, Claim 13 or Claim 14, said method further comprising the step of exposing said blood in said convective filter means to charged membrane means for repelling selected constituents in said blood.

16. The method of Claim 12 where said step of treating said filtrate stream comprises filtering said filtrate fraction through second convective filter means to provide an intermediate fraction having intermediate molecular weight components and light fraction having low molecular weight components.

17. The method of Claim 12, where said treatment step comprises discarding said intermediate fraction.

18. A method for removing plasma from blood, comprising the step of filtering said blood through filter means comprising spiral filtrate collection means for separating said blood into a plasma fraction and a cellular fraction.

19. An apparatus for the filtration of a complex fluid comprising cellular material, comprising filtration means for separation of said fluid into a heavy fraction including said cellular material and into a complex filtrate, said filtration means comprising spiral filtrate collection means.

20. An apparatus for the filtration of a complex feed fluid comprising cellular material, comprising filtration means for separation of said fluid into a heavy fraction including said cellular material and into a complex filtrate, said means comprising spiral geometry filtrate collection means and feed fluid flow means substantially parallel with said spiral geometry filtrate collection means for maintaining the output of said filtrate fraction substantially constant with respect to the input of said complex feed fluid.

21. A method for filtering cellular components from a complex feed fluid, comprising the steps of passing said feed fluid parallel to membrane means which substantially excludes said cellular components while passing a filtrate fraction, and collecting said filtrate fraction through spiral geometry filtrate collection means.

22. A method for removing predetermined components from blood, comprising the step of filtering said blood through filter means comprising spiral filtrate collection means for separating said blood into a heavy fraction having high molecular weight components and a filtrate fraction having lower molecular weight components than said heavy fraction, said filter means having ultrasonic means for avoiding clogging of said filter means in order to allow said filter means to continue to separate said blood into said heavy fraction and said filtrate fraction and for maintaining said filtrate fraction at a substantially constant rate.

23. A method for removing predetermined components from blood, comprising the step of filtering said blood through filter means comprising spiral filtrate collection means for separating said blood into a heavy fraction having high molecular weight components and a filtrate fraction having lower molecular weight components than said heavy fraction, said filter means having charged means for avoiding clogging of said filter means in order to allow said filter means to continue to separate said blood into said heavy fraction and said filtrate fraction and for maintaining said filtrate fraction at a substantially constant rate.

24. A method for removing toxic blood components from the circulatory system of a kidney patient, including the steps of: withdrawing blood from said patient; filtering said blood through filter means comprising spiral filtrate collection means to achieve continuous high efficiency separation of said blood into a heavy fraction having high molecular weight components with cells and a filtrate fraction having lower molecular weight components than said heavy fraction, said filter means having ultrasonic means for avoiding clogging of said filter means in order to allow said filter means to continue to separate said blood into said heavy fraction and said filtrate fraction and for maintaining said filtrate fraction at a substantially constant rate; treating said filtrate stream to remove said toxic blood components; and returning said treated filtrate stream and said heavy fraction to the circulatory system of said patient.

25. A method for removing toxic blood components from the circulatory system of a kidney patient, including the steps of withdrawing blood from said patient; filtering said blood through filter means comprising spiral filtrate collection means to achieve continuous high efficiency separation of said blood into a heavy fraction having high molecular weight components with cells and a filtrate fraction having lower molecular weight components than said heavy fraction, said filter means having charged means for avoiding clogging of said filter means in order to allow said filter means to continue to separate said blood into said heavy fraction and said filtrate fraction and for maintaining said filtrate fraction at a substantially constant rate; treating said filtrate stream to remove said toxic blood components; and returning said treated filtrate stream and said heavy fraction to the circulatory system of said patient.

26. A method for removing plasma from blood, comprising the step of filtering said blood through filter means comprising spiral filtrate collection means for separating said blood into a plasma fraction and a cellular fraction, said filter means having ultrasonic means for avoiding clogging of said filter means in order to allow said filter means to continue to separate said blood into said plasma fraction and said cellular fraction and for maintaining said plasma fraction at a

27. A method for removing plasma from blood, comprising the step of filtering said blood through filter means comprising spiral filtrate collection means for separating said blood into a plasma fraction and a cellular fraction, said filter means having charged means for avoiding clogging of said filter means in order to allow said filter means to continue to separate said blood into said plasma fraction and said cellular fraction and for maintaining said plasma fraction at a substantially constant rate.

28. A method for filtering cellular components from a complex feed fluid, comprising the steps of passing said feed fluid substantially parallel to membrane means which substantially excludes said cellular components while passing a filtrate fraction, and collecting said filtrate fraction through spiral geometry filtrate collection means, said membrane means having ultrasonic means for avoiding clogging of said membrane means in order to allow said membrane means to continue to exclude said cellular components while passing a filtrate fraction and for maintaining said filtrate fraction at a substantially constant rate.

29. A method for filtering cellular components from a complex feed fluid, comprising the steps of passing said feed

substantially parallel to membrane means which substantially excludes said cellular components while passing a filtrate fraction, and collecting said filtrate fraction through spiral geometry filtrate collection means, said membrane means having charged means for avoiding clogging of said membrane means in order to allow said membrane means to continue to

exclude said cellular components while passing a filtr
fraction and for maintaining said filtrate fraction a
substantially constant rate.

EDITORIAL NOTE

The applicant failed to renumber the amended claims in accordance with Section 205 of the Administrative Instructions.

In the absence of any specific indication from the applicant as to the correspondence between original and amended claims, these claims are published as filed and as amended.

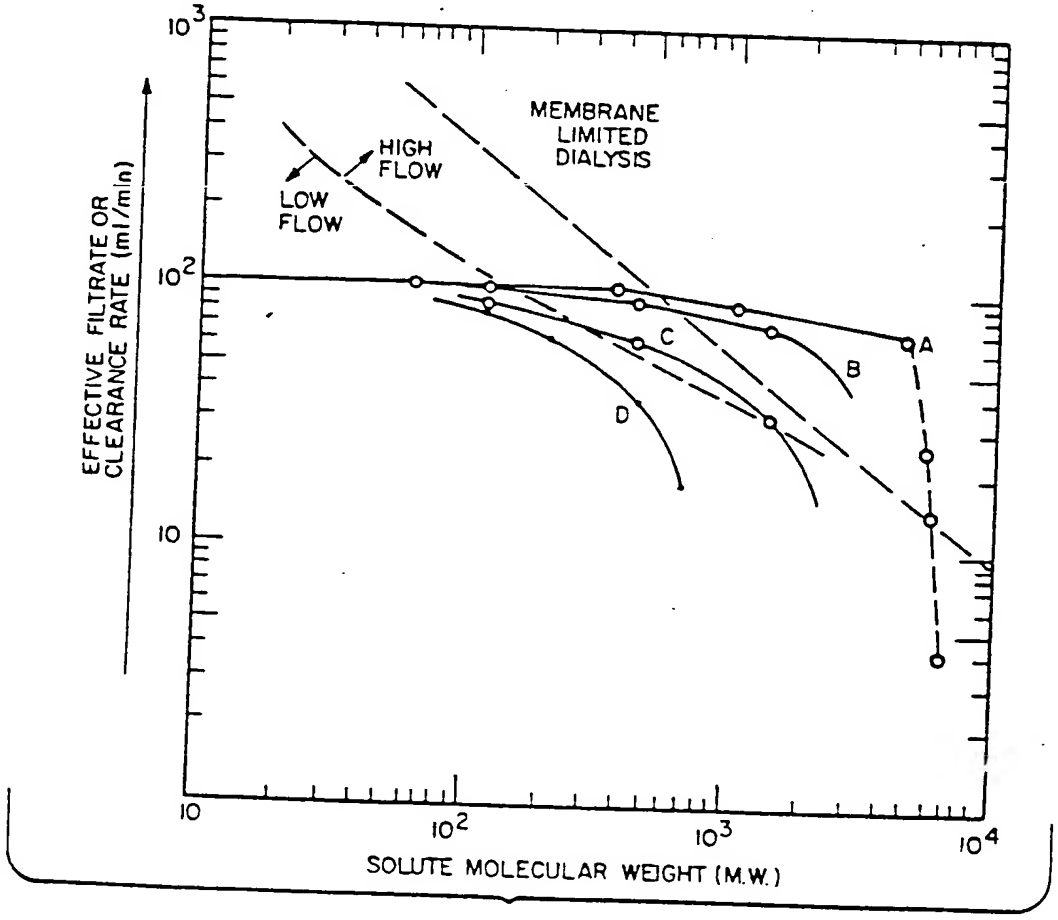


FIG-5

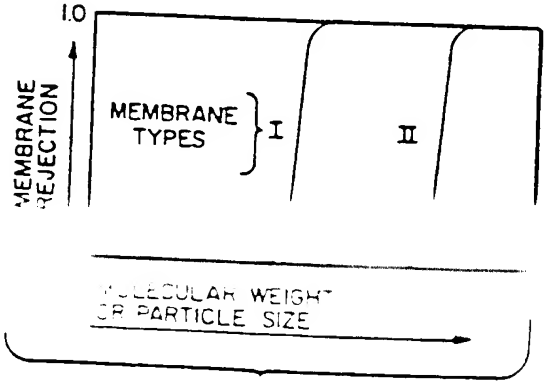


FIG-1

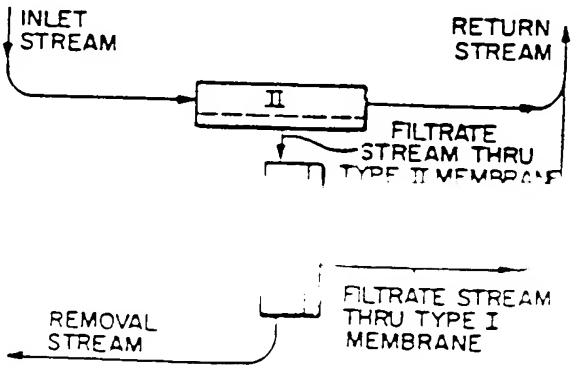


FIG-2

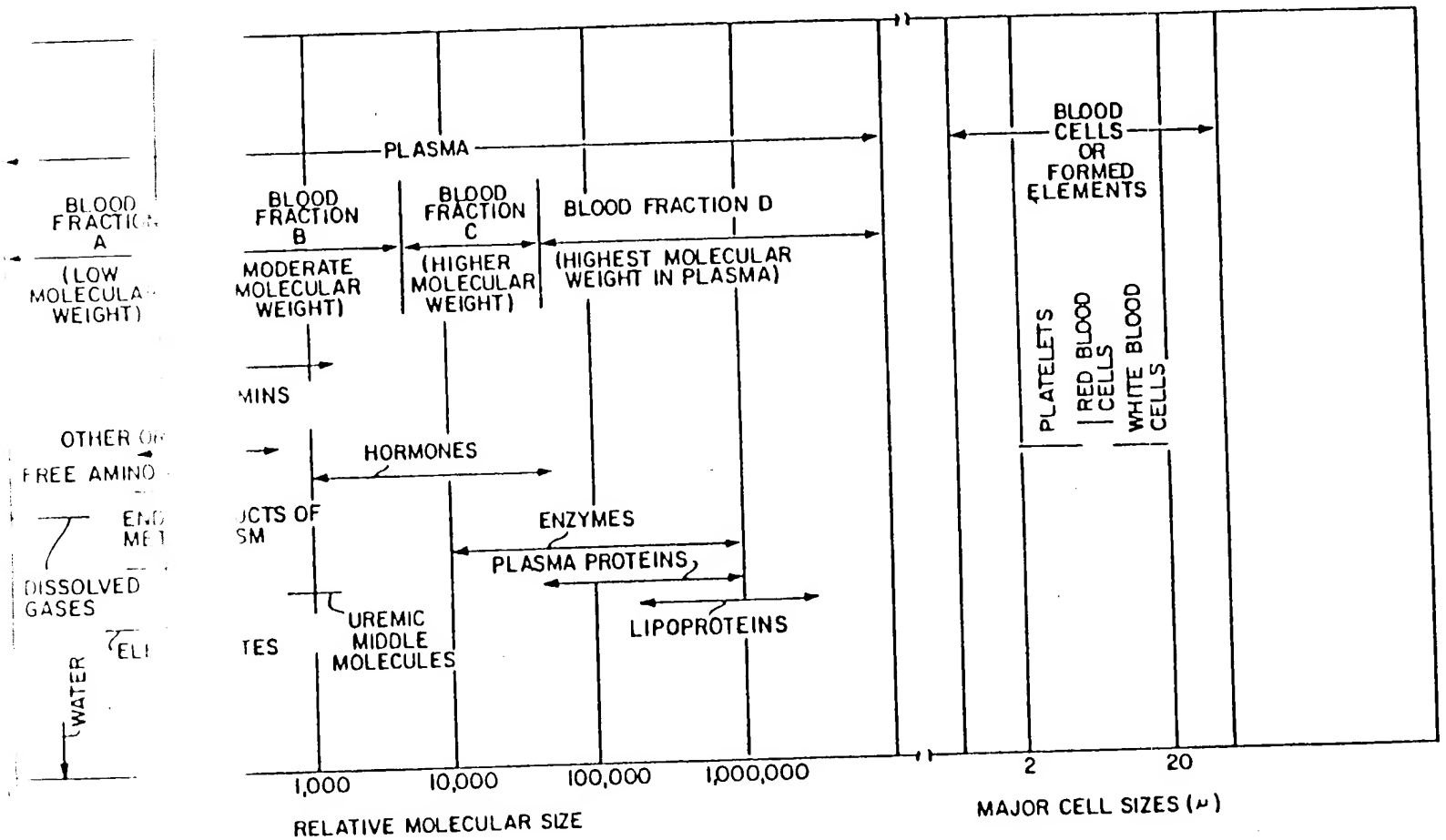
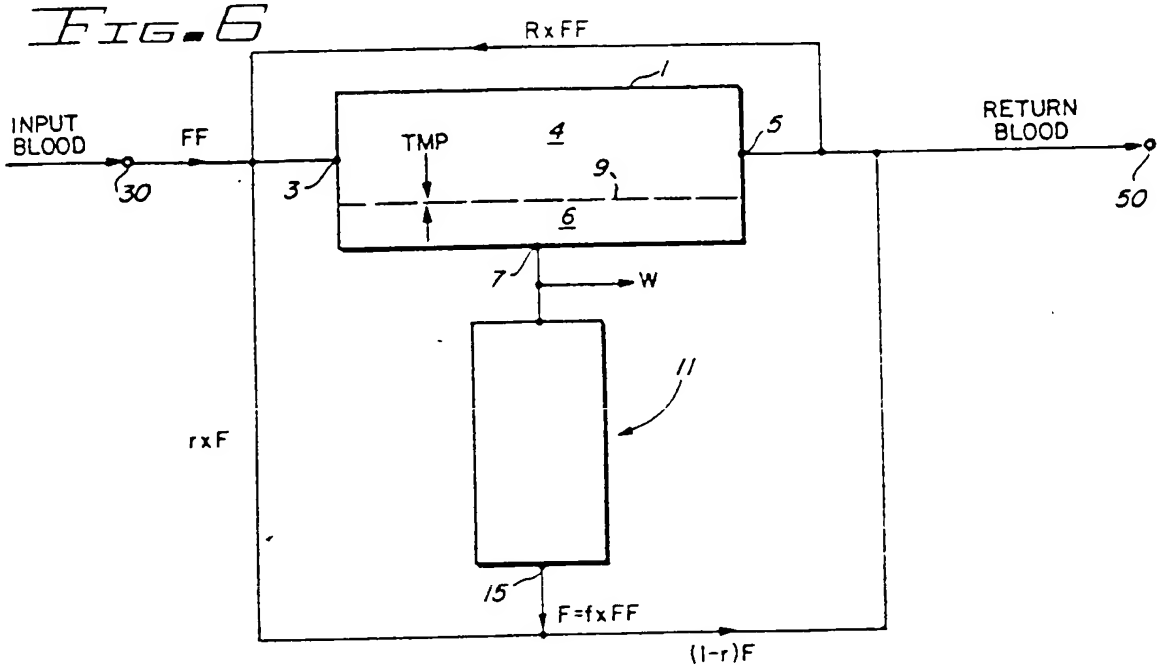
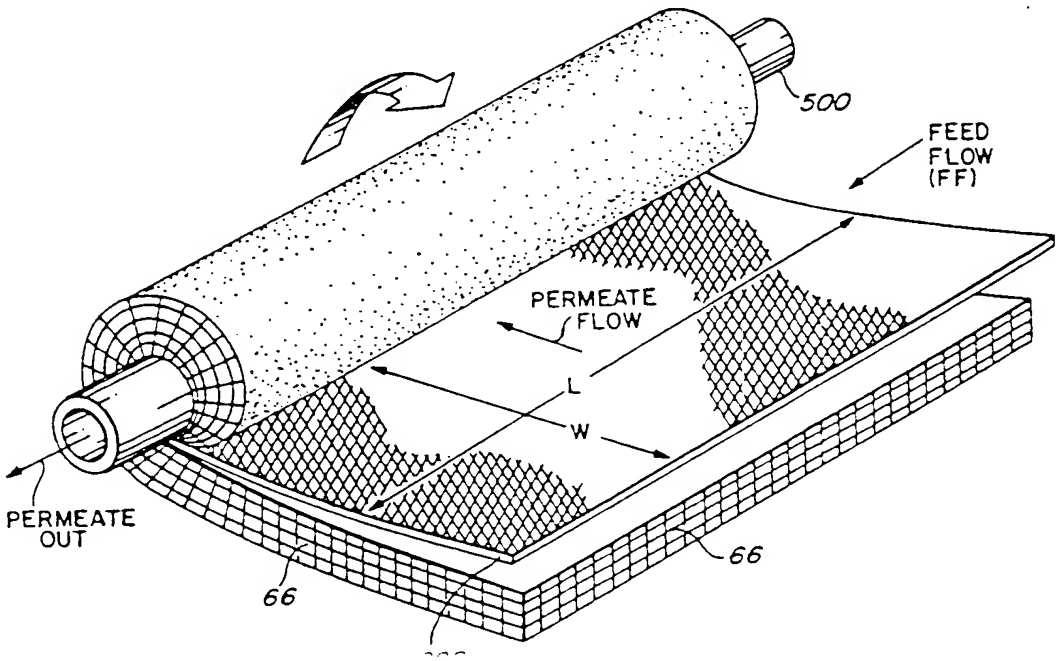


Fig-3

FIG. 6





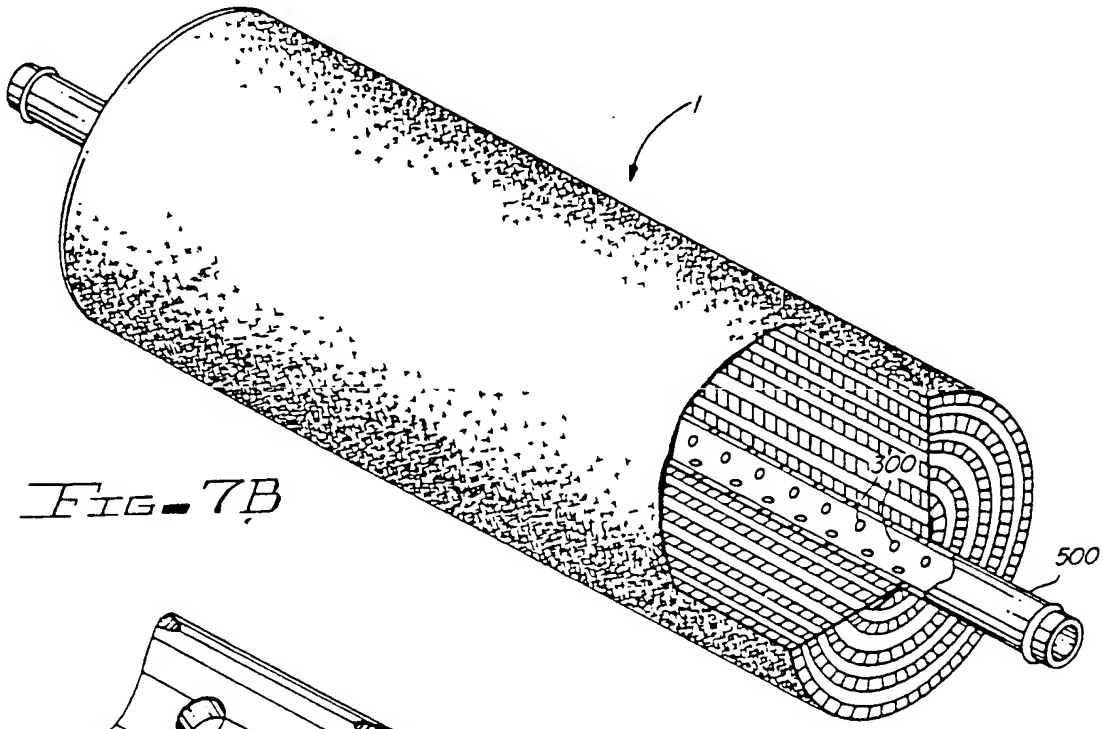


FIG-7B

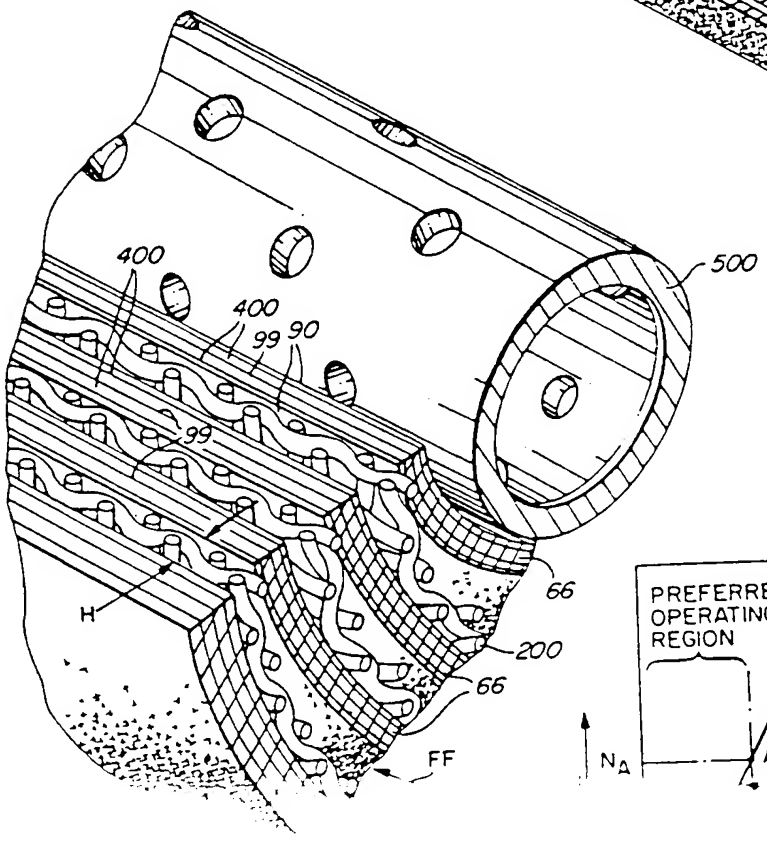
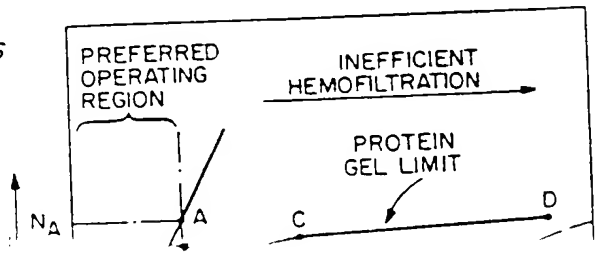
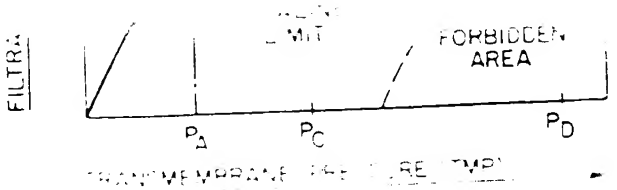


FIG-4





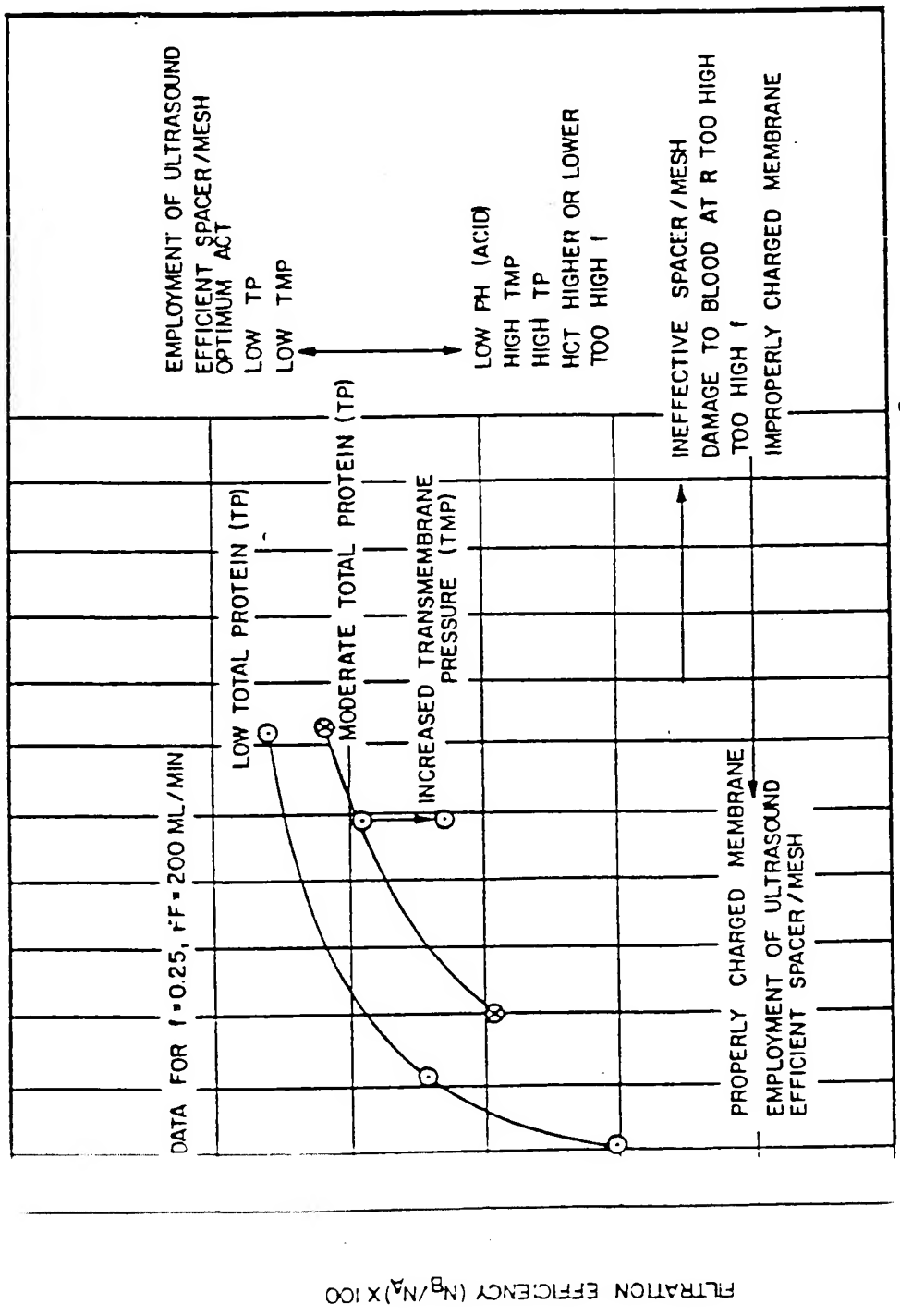


Fig-8

INTERNATIONAL SEARCH REPORT

International Application No PCT/US82/00449

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

INT. CL.[3] B01D 13/00, B01D 31/00
U.S. CL. 210/637,641,651,195.2,259,335,388,433.2, 295

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	210/636,637,641,644-651,767,779,790,805,806,195.2 210/257.2,259,295,321all,335,388,433all,455,456,927

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	US, A 3,705,100 PUBLISHED 05 DECEMBER 1972, BLATT ET AL.	1,2,4-6,10-18 20,24,26
X	US, A 3,579,441 PUBLISHED 18 MAY 1971, BROWN.	1,3-5,7-9,11-1 19-21,24,25
X	US, A 4,125,462 PUBLISHED 14 NOVEMBER 1978, LATTY.	10
A	US, A, 3,367,504 PUBLISHED 06 FEBRUARY 1968, WESTMORELAND.	1-21,24-26
A	US, A, 3,483,867 PUBLISHED 16 DECEMBER 1969, MARKOVITZ.	1-21,24-26
A	N, TRANSACTIONS OF THE AMERICAN SOCIETY OF ARTIFICIAL INTERNAL ORGANS, VOLUME 14, ISSUED 27 APRIL 1978, W.J. DORSON ET AL, QUANTITATION OF MEMBRANE-PROTEIN-SOLUTE INTERACTIONS DURING ULTRAFILTRATIONS, PAGES 155-161.	1-21,24-26
A	N, CHEMICAL TECHNOLOGY, ISSUED JANUARY 1971, M.C. PORTER ET AL, MEMBRANE ULTRAFILTRATION, PAGES 56-63.	1-21,24-26
A	N, JOURNAL OF AGRICULTURE AND FOOD CHEMISTRY, ISSUED 1971, W.F. BLATT, MEMBRANE PARTITION CHROMATOGRAPHY: A TOOL FOR FRACTIONATION OF PROTEIN MIXTURES, PAGES 589-594.	1-21,24-26

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
17 JUNE 1982	19 JUL 1982
International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/US	David R. Sadowski DAVID R. SADOWSKI

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 22 and 23, because they relate to subject matter [12] not required to be searched by this Authority, namely:

Said claims fail to comply with PCT Rule 6.4 (a) in utilizing multiple dependent claims as the basis for multiply dependent claims.

2. [ ] Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.